IMMUNITY TO YELLOW FEVER *

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Whether the immunity produced by an attack of yellow fever is permanent or temporary is a disputed point among modern epidemiologists. Naturally a disease produced by micro-organisms, and which recovers spontaneously, must produce immunity, local or general, temporary or permanent, else one would not recover. That it is permanent has been, and is now, the opinion of American epidemiologists, and of the older generation of French and English writers who added so much to our knowledge of this disease by their observations in the West Indies and in Africa.

There was, however, a very common belief among the laity of localities in which yellow fever was endemic, that leaving such focus of endemicity for a sufficient time would restore the susceptibility to the disease. This belief is alluded to by many writers. It was, I think, universally regarded as erroneous by those *not* living in endemic areas, but given more consideration, and sometimes, I think not generally, affirmed by writers who lived in such endemic areas.

On the other hand, a commission of the Pasteur Institute, Marchoux, Salembini and Simond, working in Rio Janeiro in 1903 to 1905, state categorically that the immunity produced by an attack of yellow fever gives temporary immunity only, and that the infection is kept up in endemic centres by recurrent attacks among the indigènes. This view is reiterated by other recent French observers, and so far as recurrent attacks being common, is accepted by Seidelin, Rubert Boyce and others. Indeed, it is fair to say that this view, that recurrent attacks of yellow fever are common, is held by nearly all the writers recently engaged in investigating

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the epidemiology of yellow fever. Seidelin seems to base his belief mainly on the occurrence of sickness in men who have had yellow fever before, which attacks he pronounces to be also yellow fever on account of finding in the blood of these patients the organism he believes to be the cause of yellow fever.

When the statement above made was first quoted by Marchoux and Simond, no evidence therefor was, I think, given. A large amount is given, however, by Simond and his collaborators in the report on the epidemic at Martinique in 1908 and 1909. This report is far stronger in its implication of recurrent attacks than it is in assertions of definite recurrences in individual cases, and it is a strong report. Without criticizing it—this would require greater knowledge of the nosology and epidemiology of Martinique than I possess—it is so at variance with what I have seen in the United States, in Cuba and in Panama, that it seems advisable to give such reasons as I have for the opposite view; especially as one would suppose that in the United States, where greater intervals occur between the epidemics of yellow fever, which have also been apparently more extensive and more severe than those in Martinique, one would be more apt to find recurrent attacks than in that island.

Speaking of the immunity given by an attack of yellow fever being permanent—generally permanent only is meant. Absolute immunity given by one attack is not predicated of any disease.

Obviously the natural method of testing this question is by observation of the exposure of men who have had yellow fever to the infection of that disease, and determining if they contract it again. The existence of the infection and degree of exposure would be judged of by the proportion of cases contracted by those who had *not* had yellow fever similarly exposed to infection-controls. If a negative result is reported, the observation would be convincing in proportion to the number of supposedly immune men thus exposed; the intervals from their last attacks; the degree of exposure, and the certainty that secondary attacks did not occur among men.

Such observations are not rare, for instance at the end of 1879 there must have been a very small proportion of the population of New Orleans, Mobile, and the coast towns between them who had not suffered an attack of yellow fever in that or in previous years.

They were free from yellow fever until 1897. In that year and 1898 there were widespread epidemics, yet recurrent attacks were reported in extremely few cases in these towns in 1897 and 1898—eighteen years later. Certainly no considerable number of well-marked cases could have occurred in those years. The same is true of many other epidemics and many other towns in the United States. We can readily present, then, a large number of people having had one attack of yellow fever exposed, after sufficiently long intervals, to infections very prevalent among those who had not had yellow fever with a report of no, or extremely few, cases of yellow fever among them.

Ought not this to be convincing of the permanency—the general permanency—of the immunity? Put yourself on the other side. The first three factors in the evidence—the number of the people exposed, the lengths of the intervals and the prevalence of the infection—you will readily grant us; but I fear that a question will be raised on the last condition—the certainty that secondary cases do not occur. The question will be asked: Is it certain that yellow fever did not occur, and quite generally, among these people? It would be held that, on account of believing that one attack gives permanent protection, we would not recognise yellow fever occurring among them.

There is truth in this contention. We of my generation have accepted previous opinion on this matter, and, not having found it contradicted by obvious facts, have not examined into the matter critically. We assumed that one attack gave permanent protection. We would then have been little apt to consider an attack of sickness occurring in one who had previously had yellow fever as yellow fever unless it was either (1) well marked or (2) gave rise to yellow fever in others. The first might not be the case with light—certainly not with ephemeral—attacks, the kind which naturally would occur as secondary attacks. The second we will consider presently.

Even if a secondary attack were clearly yellow fever, one with our belief would, in the absence of good evidence to the contrary, question the diagnosis of the previously reported attack. This it is natural to do, because we know how many cases of other disease are diagnosed as yellow fever during an epidemic. I did this

in the case of an officer in this service who died of yellow fever under my care at Chandeleur, in 1890. He was reported to have had yellow fever in 1878. For the acceptance of a secondary attack it might then require that a *well-marked case* of yellow fever occur *twice* in the same person. Now, even under the doctrine of temporary immunity, this would be rare, as those who hold it also hold that there would be a lowered susceptibility from the first attack, and that if the attacks were not very far apart the second one would be mild—or very mild—and that is reasonable. You can see, then, that we have not been in a proper state of mind to examine this part of the question critically, and, indeed, I have not done so. Even allowing for this, the number of second attacks reported in places in which yellow fever occurs only in epidemics—the places in which we would be most apt to expect them—are exceedingly rare. They are reported, however, and the recognition of such cases is proof that our eyes are not so blinded by our belief that we cannot recognize second attacks of yellow fever if they be plain enough. I have seen three cases of yellow fever in people who were said to have had a previous attack. In two of them the evidence for the first attack seemed to me to be slight; the third I could not enquire into.

When we come to individual cases, the men we knew who had yellow fever at one epidemic and who were exposed to it a second time after a considerable interval—and I have seen many such—the most I can say is that, in my acquaintance, I have not known a second attack *to be reported*. Drs. P. and W. had yellow fever in Memphis, Tenn., in 1879 and 1878, respectively, and were not exposed again until 1897 at Edwards, Miss., after intervals of eighteen and nineteen years. P. was not reported to have yellow fever at Edwards, but he was sick there with a diagnosis of malarial fever which was prevalent, and to which he was subject. W. was not sick at all. Lieutenant G. had yellow fever in Brownsville, Texas, in 1882; no exposure until 1898 at Siboney, sixteen years later. He was sick at, or after leaving, Siboney with a diagnosis of malarial fever which was extremely prevalent. He did have malaria; plasmodia demonstrated, and recurrent attacks for about a year; but that by no means excludes the possibility of yellow fever. Dr. P., of this service, had yellow fever at Chattanooga,

Tenn., in 1878, next exposure was at Panama in 1903, twenty-six years interval. He was, after nearly a year's residence in good health at Panama City, sick at Ancon Hospital in 1904, with what I myself thought was going to develop into a severe attack of yellow fever, until the second day, when the case showed itself to be clearly dengue—I am satisfied that this case *was* dengue, although it was before we knew the diagnostic value of the blood picture; for it was a severe case, and such are well marked. The terminal eruption, too, was typical, yet you see that one believing that secondary cases are common, might find fault with the diagnoses of all the above. I could add to my knowledge, I think, from twenty-five to fifty cases to the above; but they would be more or less similar. Some did not get sick on the second or subsequent exposure, yet that is not convincing. Some people who have never had yellow fever go through an epidemic unscathed. Also light attacks might well escape unnoticed.

The difficulty is that we recognize no sign as pathognomonic for all cases of yellow fever, the mild and ephemeral as well as the severe. It is true that Seidelin claims to have such a sign in his *Paraplasma flavigenum*, and also to have demonstrated it in a secondary (ephemeral) case of yellow fever in himself and in others, some of whom showed no signs of illness, i.e., were 'carriers.' Without in any way pronouncing on the validity of his claims, yet until his primary contention is confirmed—the transference to guinea-pigs is certainly discredited—we cannot accept the existence of his bodies as pathognomonic of yellow fever, and hence as proving a second attack.

The second test, that yellow fever was communicated to others from cases of sickness of men who had previously had yellow fever, is again hard for us to apply.

When you consider how freely men 'protected by a previous attack of yellow fever' have been allowed to move from places virulently infected with that disease into susceptible communities in the United States, and how many hundreds of times this has occurred during epidemics, you would think we should have satisfactory data on this subject, positive or negative. If not immune to yellow fever, some of these men should have contracted it, and developed it in an infectable but not infected place, and

even if not diagnosed, it should have infected mosquitos and spread to others in whom the diagnosis would be easy. An epidemic cannot be hidden.

I know of no evidence that this has occurred, yet the evidence to the contrary has not been scrutinized critically. Since we did not believe that secondary cases of yellow fever occurred—or occurred very rarely—if an outbreak occurred we would be little apt to impute conveyance of yellow fever to any sickness of indeterminate nature occurring among people who were 'protected by a previous attack of yellow fever.' Almost any other hypothesis would be accepted to explain it, or it would be left unexplained. Indeed, in times of epidemics, there are so many ways in which infection can be introduced that an outbreak, of which we are not able to explain the introduction, is not to be wondered at.

To use this test, then, we must depend upon the scrutiny of exposure of susceptible communities to cases of sickness of such 'protected' men who had themselves been exposed to yellow fever, and under such conditions *that other sources of exposure to the community are excluded*. Opportunity for this would rarely occur during an epidemic.

As evidence of attacks of yellow fever do not recur among such 'protected' people, these observations, to be convincing, must be on a large scale, there must be many failures of susceptible communities thus to receive infection. This would be negative testimony, and convincing only in proportion to its mass. I know of no positive observations on this subject. It seems useless to relate the twenty-five or thirty—maybe fifty—negative observations I could give you. They are not convincing.

Positively, however, we have in the passenger traffic of the Plant Steamship Line data of sufficient mass to be worth considering. From 1889 to 1897, inclusive, nine years, there was no bar to the transit on these vessels from Havana to Key West and Tampa of passengers 'protected from yellow fever by a previous attack of ten years' residence in an endemic focus,' and a great many of them came: Cubans on their ten years' residence, and Americans on a certificate of previous attack. There were cigar factories in Key West, Tampa and Jacksonville all manned by Cuban employees. There were generally two vessels per week, part of the

time three vessels. Havana was about six hours from Key West and twenty-four from Tampa. I am unable to give the exact number of these passengers, on account of the destruction of the records of the State Board of Health of Florida by fire. Such reports of this Board as are available to me give the number of such passengers as follows:—

Tampa Bay Quarantine

1891—May 1st to October 31st	2,620
1892—May 1st to October 31st	2,684
1893—May 1st to October 31st	2,449
1894—May 1st to October 31st	3,681
Four years	11,434

Key West

1893—August, September and October ...	3,134
1894—May 1st to October 31st	7,556
One and one-half years	10,690

In addition we have a Havana record showing that about 3,420 passengers were certified for Tampa in 1895 (2,850 from May to October 1st). At the above rate the entries at Tampa would for nine years be 25,726, call them twenty thousand, to be conservative. For the short time of which we have record Key West had double as many entries as Tampa, and this is in accord with my observation at the time and in 1899. It will be very conservative, then, to put the number of so-called 'immune passengers' at thirty thousand for the nine years—it was more likely fifty thousand or sixty thousand. Many entries, naturally, were the same people going backward and forward between Havana and Florida ports. Now remember that this very considerable number of people, and I have given you minimal figures, came from a city where yellow fever was endemic; that they came in hot weather to towns where *Aëdes calopus* (*Stegomyia*) were abundant and active, and where people susceptible to yellow fever were also abundant. If, then, any considerable portion of them after arrival had been infective to *Aëdes calopus*

(*Stegomyia*), I cannot but think that there would have been at least one outbreak of yellow fever in Florida during these nine years. There was none.

Were these people so exposed in Havana that any considerable number of them would certainly have contracted yellow fever if they were susceptible to that disease? Let us see. That those who had not had yellow fever were liable—and very liable—to contract that disease from exposure in Havana at this time was evidenced by the history of vessels from that port whose personnel had *not* had yellow fever. They frequently brought cases of yellow fever to our quarantine station. In 1895, at the Dry Tortugas, I had thirteen cases of yellow fever on Havana vessels out of a crew list of less than 450 men. Indeed, the crew list of men exposed to infection in Havana was not over half of 450, as the steamers lay in a safe part of the harbour—Criscona—and allowed only a very few men ashore, and were practically free from fever. It occurred (with one exception) on vessels which had lain on the Havana side of the harbour. Unquestionably, then, those susceptible to yellow fever could contract it in Havana at this time.

Compare these observations:—

(1) Four hundred and fifty people who had not had yellow fever from Havana gave thirteen cases of yellow fever, every one of which should have been infective to *Aëdes calopus* (*Stegomyia*).

(2) Thirty thousand people from the same place during a period covering the same time give no evidence of infecting *Aëdes calopus* (*Stegomyia*); certainly gave no rise to an outbreak in the susceptible communities to which they moved.

You may consider this *proof*; there may not be enough of it to satisfy you; but the mass of this evidence, negative as it is, is sufficient until the contrary is proven to confirm me in my belief that, for sanitary purposes, the immunity conferred by one attack of yellow fever is permanent; that recurrent attacks infective to *Aëdes calopus* (*Stegomyia*) do not occur, and that we are justified in basing our sanitary measures thereon. It should at least prevent your acceptance of the doctrine that the immunity conferred by an attack of yellow fever is quite temporary, and that subsequent attacks infective to *Aëdes calopus* (*Stegomyia*) are common, and that sanitary measures based on the contrary opinion are unsafe. This

observation—the passenger traffic of the Plant Line—is also inconsistent with the existence of 'carriers' as a common phenomenon capable of infecting *Aëdes calopus* (*Stegomyia*)—against which, however, a stronger argument can be made.

I said 'until the contrary is proven,' because if it be ever shown that an organism causative of yellow fever occurs in men who have had previous attacks of this disease, and is conveyable from them by *Aëdes calopus* (*Stegomyia*) mosquitos to other men producing yellow fever in them, I will count the contrary proven. I well know how much more determinative are the results of experimental than of epidemiological investigation; yet in this disease it was, I believe, the latter that gave the key to the problem, which determined the direction of the experimental investigation which demonstrated the method of conveyance. I do not mean that this is the only means of demonstration. Even if the causative micro-organism is not demonstrated, the frequent recurrence of clinical yellow fever in those who have had one attack, as indicated in the Martinique epidemic, *sufficiently verified* would be proof.

There are other epidemiological investigations which are at least consistent with a doctrine of permanent immunity, such as the disappearance of yellow fever from small and moderate-sized towns in the Tropics which received few susceptible immigrants. I do not mean that this always occurs; but it is by no means rare in America. The great decrease of infection in Havana in 1899, due to the falling off of immigration in the previous years, is also consistent with it. This was shown in the small number of cases of yellow fever in the spring and summer of that year as compared with normal years, although the town was full of Americans, who went everywhere, and with *Aëdes calopus* (*Stegomyia*).

As I have said, against the existence of carriers the evidence is stronger than that against secondary attacks; or, rather, the data on which it rests—again negative—is greater in amount.

There is no record of yellow fever being contracted in New Orleans during the years 1884 to 1896, inclusive. During this period, thirteen years, the crews and passengers of many vessels from yellow fever ports were admitted to this city. During the quarantine season—May 1st to October 31st, the only part of the year that we will consider—this personnel was held a short time in

quarantine prior to admission. I can find no records of the number of this personnel, but I find, supplying a few gaps by proportionate estimates, that during this period there were held for yellow fever at the New Orleans quarantine nineteen hundred and ninety-four steam vessels and four hundred and seventeen sailing vessels. We cannot well make the crews of the former less than sixty thousand (59,820), or of the latter less than six thousand (6,250), a conservative estimate of the passengers—from Havana mainly—would put them at six thousand (6,700)—a total of over seventy thousand (72,775); there were more likely ninety thousand.

If carriers were at all common among this class of people, with so large a number of people we would expect to find a considerable number. Now the introduction of any considerable number of people into New Orleans infective to *Aëdes calopus* (*Stegomyia*) during the summer time should have been followed by outbreaks of yellow fever. As I have said, there was none. There could have then been no considerable number of people infective to *Aëdes calopus* (*Stegomyia*) among them. This evidence, then, must be added to that just adduced as against the existence of carriers—at least among the personnel of vessels from yellow fever ports in sufficient numbers to affect sanitary measures at United States ports.

What has been said of New Orleans applies equally to Galveston, Mobile, Pensacola and Savannah; and adding the number of ships' personnel from yellow fever ports admitted into these cities without causing any outbreak of yellow fever among them, the total must be well over one hundred thousand.

It is fair to say that only a small proportion of this personnel, especially of the crew, would be expected to show carriers under the circumstances in which they would be expected to exist, i.e., among people who had suffered from yellow fever and were constantly exposed to it. Yet there were a large number, even if a small proportion, of such men aboard vessels from Havana, Spaniards, Manilla men, Italians and Americans.

It is to be noted that the term 'carrier' is here used in a sanitary sense only, i.e., a vector, one infective to *Aëdes calopus* (*Stegomyia*), one from whom the disease can be conveyed to other people by the natural method.

SUMMARY

Is the immunity conferred by an attack of yellow fever permanent, or are subsequent attacks common?

The first is the view held by observers in countries where yellow fever prevails epidemically. The second has been the belief of many—especially of the laity—in endemic foci. It is now held by many eminent investigators who have worked in endemic foci of yellow fever; by the majority of recent writers, I think.

The evidence for the permanence of this immunity ought to be most abundant in places where yellow fever occurs in epidemics, and much is brought forward—negative from the nature of the case. This evidence would rarely be satisfactory to those holding a contrary view, because the belief of the physicians in such places that this immunity is permanent would render them little apt to recognize secondary attacks unless they were well marked, and they would rarely be well marked.

There are, however, some epidemiological data which—as far as they go—are evidence against the occurrence of secondary cases infective to *Aëdes calopus* (*Stegomyia*).

Thus, between the years 1888 and 1898, there entered Florida ports over thirty thousand people certified as 'Protected from yellow fever by previous attack or ten years' residence in an infected focus.' They came during the summer, May 1st to October 31st, from Havana, where yellow fever prevailed during this time, to Key West and Tampa—towns full of *Aëdes calopus* (*Stegomyia*) and of people susceptible to yellow fever. The time of passage was about eight hours to Key West, and twenty-four to Tampa. As no yellow fever developed in Florida during this period, there should have been no considerable number of secondary attacks infective to *Aëdes calopus* (*Stegomyia*) among these people.

That yellow fever could be readily contracted from Havana by people susceptible to it is shown by the fact that during this time four hundred and fifty people from Havana, not certified as immune to yellow fever, yielded thirteen cases of yellow fever at a quarantine station.

As thirteen cases of yellow fever, any one of which should have been infective to *Aëdes calopus* (*Stegomyia*), occurred among

four hundred and fifty men who had not suffered from one attack, it would seem that if recurrent attacks were common, enough cases should have occurred among the thirty thousand to have produced an outbreak in Florida. There was none.

The above is also evidence that yellow fever carriers are not as common as are alleged by some modern observers; as is also the fact that the quarantine stations of the United States have for many years passed in a large number of people—well over a hundred thousand—from yellow fever ports with no evidence of their having infected *Aëdes calopus* (*Stegomyia*) in the United States.